

## REMARKS

The amendments to the specification are pursuant to a Petition to Accept an Unintentionally Delayed Priority Claim. The amendments to the claims find support in the specification and claims as originally filed. The amendments to Claims 126 and 127 find support in the specification, for example, at page 55, line 6. The amendment to Claim 132 finds support in the specification, for example, at page 10, line 27. No new matter is added by way of the amendments.

Claims 124-132 are pending and under consideration in the application.

Claims 126 and 127 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite; Claims 124-132 stand rejected under the judicially created doctrine of obviousness-type double patenting; Claims 124-130 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over U.S. Patent No. 6,133,426 to Gonzalez et al. (hereafter "Gonzalez") in view of Zapata et al. (hereafter Zapata); Claims 124-130 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over U.S. Patent No. 5,695,760 to Faanes et al. (hereafter "Faanes") in view of Zapata and U.S. Patent No. 5,766,897 to Braxton et al. (hereafter Braxton); Claims 124-132 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Faanes in view of Zapata and Braxton and further in view of Carter et al. (hereafter "Carter") and U.S. Patent No. 5,620,689 to Allan et al. (hereafter "Allan"); Claims 124-132 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Koumenis et al. (hereafter "Koumenis") in view of Carter and Allan. Claim 132 stands objected to as containing a typographical error.

### The Rejections under 35 U.S.C. § 112, second paragraph

Claims 126 and 127 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner suggested that it is not clear how a Fab, Fv or scFv could have a hinge region cysteine. As amended, Claims 126 and 127 do not recite Fab, Fv or scFv fragments. Applicants respectfully submit that Claims 126 and 127 are not indefinite.

Accordingly, Applicants respectfully submit that the rejections of Claims 126 and 127 under 35 U.S.C. §112, second paragraph are overcome.

**The Provisional Double-Patenting Rejections**

Claims 124-132 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over Claims 1, 20, 25, 26, 28, 31, and 32-36 of copending Application Serial No. 09/726,258 in view of Carter and Allan. Claims 124-132 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over Claims 1 and 27 of copending Application Serial No. 09/355,014 in view of Carter et al. and Allan et al.

Applicants respectfully traverse these rejections. As these rejections are provisional, applicants respectfully await an indication of allowable subject matter in the present case, at which time a determination of whether common subject matter has been claimed in both applications, and as to the suitability of a Terminal Disclaimer may be assessed.

**The Requirement to Show Common Ownership**

The Examiner has required a showing that the present application and Application Serial No. 09/355,014 were commonly owned at the time the invention in the present application was made. Application Serial No. 09/355,014 and also Application Serial No. 09/726,258 were commonly owned at the time the invention in the present application was made. Applicants note that the present application, 09/489,394, is assigned to Genentech, Inc. The assignment was recorded with the U.S. Patent and Trademark Office on October 3, 2000 at reel/ frame: 011202/0462.

Application Serial No. 09/355,014 is also assigned to Genentech, Inc. The assignment was recorded with the U.S. Patent and Trademark Office on January 16, 2001 at reel/frame: 011458/0859.

Application Serial No. 09/726,258, a continuation of Application Serial No. 09/726,258, is also assigned to Genentech, Inc. The assignment of its parent

application, Application Serial No. 09/234,182, was recorded with the U.S. Patent and Trademark Office on May 20, 1999 at reel/frame: 01002/0349.

Photocopies of the assignment recordation documents are enclosed.

Accordingly, the applications being commonly assigned at the time the invention was made, Applicants respectfully submit that the requirement to show that the "conflicting" inventions were commonly owned at the time the invention in this application was made has been fulfilled.

**The Rejections of Claims 124-130 under 35 U.S.C. §103(a)**

Claims 124-130 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over U.S. Patent No. 6,133,426 to Gonzalez et al. (hereafter "Gonzalez") in view of Zapata et al. (hereafter Zapata).

With the present amendment, and as requested in a Petition to Accept an Unintentionally Delayed Priority Claim (copy enclosed), Gonzales is not a proper reference since it is a co-pending application to which priority has been claimed. As noted in the Petition, Gonzales and the present application share a common inventor and are assigned to the same assignee, Genentech, Inc. In addition, with the present amendment, and as requested in the Petition, the present application claims priority to Application Serial No. 08/844,444, filed February 21, 1997, so that Gonzalez would not be prior art even if it were not a priority document of the present application.

Accordingly, Gonzalez et al. not being a proper reference, the rejection of Claims 124-130 under 35 U.S.C. §103(a) as allegedly being obvious over Gonzalez in view of Zapata is reduced to being a rejection of Claims 124-130 under 35 U.S.C. §103(a) as allegedly being obvious over Zapata.

In order to establish a *prima facie* case of obviousness, there must be: 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art,

and not based on the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

However, Zapata discusses that the nonspecific clearance of an antibody Fab fragment with a molecular weight of 49 kD can be decreased by addition of a 10 kD PEG moiety, and that as long as the effective molecular size is below 70 kD, clearance decreases as molecular weight increases. Zapata also notes that this might not apply to molecular sizes that exceed the glomerular filtration cutoff size of 70 kD. Thus, Zapata does not provide all the elements of the claimed invention; it does not suggest or motivate a combination with another proper reference to provide the claimed invention; and, failing to provide all the elements and failing to provide suggestion or motivation to provide the claimed invention, Zapata does not provide any reasonable expectation of success even if it were to be so combined.

Applicants thus respectfully submit that Zapata, discussing a PEG moiety of 10 kD and suggesting an upper molecular size limit of 70 kD, does not make obvious the present claims, which are directed to antibody fragment conjugates with nonproteinaceous polymer molecule(s) having molecular weights of at least 20 kD, and an apparent molecular weight as determined by size exclusion chromatography of at least about 500 kD. Accordingly, Applicants respectfully submit that the rejections of claims 124-130 under 35 U.S.C. §103(a) as allegedly being obvious over Gonzalez in view of Zapata are overcome.

#### The Rejections of Claims 124-130 under 35 U.S.C. §103(a)

Claims 124-130 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over U.S. Patent No. 5,695,760 to Faanes in view of Zapata and U.S. Patent No. 5,766,897 to Braxton.

Zapata has been discussed above. Faanes is presented by the Examiner as discussing methods and modifications of antibodies with attachment of PEG molecules to the antigen binding fragments, and as discussing anti-CD 18 antibodies, humanization, fragments, including fragments modified to contain about 2-15 molecules of PEG with PEG of 5 kD to "higher molecular weight PEGs" (the Examiner citing

column 14, lines 9-10). Braxton is presented by the Examiner as discussing methods for PEGylating proteins by attaching a PEG molecule via the thiol on a free cysteine, and as discussing that the molecular weight of the attached PEG may be from 0.2 to 20 kD.

However, as noted by the Examiner, "Faanes does not teach attachment of PEG to the hinge region of the antibody fragment or that the PEG is specifically 20 kD" (page 10, lines 11-12 of the instant Office Action).

Faanes discusses the use of antibody PEGylation in order to reduce the immunogenicity of a PEG-derivatized antibody in an animal. Faanes, discussing full-length antibodies, does not discuss antibody fragment conjugates. Faanes discusses PEGylation of full-length anti-ICAM antibody with 5 kD PEG at, e.g., column 21-23. However, out of 17 exemplified conjugates, only 3 were found to have reduced immunoactivation in immunized animals as compared to the underivatized antibody; these three were not characterized as to possible shared structural features, although the use of 5 kD PEG is referred to as "preferred" throughout the disclosure. Thus, discussing 5 kD as preferred, and providing no suggestion of an apparent molecular weight of at least about 500 kD, Faanes provides no motivation for one skilled in the art to prepare conjugates with an apparent molecular weight of at least about 500 kD.

Braxton discusses PEG molecules attached to proteins; the proteins are not identified as being antibodies. As discussed above, Braxton discusses PEG molecules of a molecular weight of between 0.2 kD and 20 kD, that is, of at most 20 kD. Braxton does not discuss molecular size, nor apparent nor effective molecular size. Braxton does not suggest or discuss conjugates having an apparent molecular weight of at least about 500 kD. Accordingly, Braxton provides no suggestion or motivation to conjugate PEG molecules of at least about 20 kD to antibody fragments to obtain antibody fragment conjugates having an apparent molecular weight of at least about 500 kD.

Applicants respectfully note that Applicants have discovered that conjugation of nonproteinaceous polymers to antibody fragments leads to surprisingly and unexpectedly large increases in the apparent molecular weight of the conjugates, so

that, for example, conjugation of a 20 kD nonproteinaceous polymer to an antibody fragment provides a conjugate of an apparent molecular weight, as determined by size exclusion chromatography, of at least about 500 kD.

As discussed above, Zapata, discussing 5 kD and 10 kD molecules, suggests that larger molecular weights (e.g., above 70 kD) might not be effective; Faanes discusses 5 kD PEG conjugates; and Braxton discusses conjugates with PEG having a molecular weight of up to 20 kD. None of the cited references discuss antibody fragments conjugated with non-proteinaceous polymer molecules of at least about 20 kD and having an apparent molecular weight of at least about 500 kD. None of the cited references discusses the surprising results disclosed by applicants.

Thus, the cited references fail to discuss and fail to provide any suggestion of at least the elements of the claimed invention of conjugation of antibody fragments with non-proteinaceous polymer molecules having actual molecular weights of at least 20 kD to provide a conjugate having an apparent molecular weight of at least about 500 kD as determined by size exclusion chromatography. Failing to suggest at least these elements, the cited references provide no motivation to be combined to provide the claimed invention. Failing to provide at least these elements, and failing to provide motivation to combine the references in an attempt to provide the claimed invention, the cited references fail to provide a reasonable expectation of success for such a combination.

Accordingly, Applicants respectfully submit that rejections of Claims 124-130 under 35 U.S.C. §103(a) as allegedly being obvious over Faanes in view of Zapata and Braxton are overcome.

**The Rejections of Claims 124-132 under 35 U.S.C. §103(a)**

Claims 124-132 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Faanes in view of Zapata and Braxton and further in view of Carter and U.S. Patent No. 5,620,689 to Allen.

Faanes, Zapata, and Braxton have been discussed above. The Examiner noted that Faanes does not teach an antibody to HER2 or to CD 20. Carter is presented by the Examiner as discussing a conjugate of PEG to an anti-HER2 antibody, and Allan is presented by the Examiner as discussing a conjugate of PEG to an anti-CD20 antibody.

However, as discussed above, Faanes, Zapata and Braxton fail to provide all the elements of the claimed invention, fail to provide suggestion or motivation to attempt to combine them to provide the claimed invention, and fail to provide a reasonable expectation of success were they to be combined. Carter and Allan together fail to make obvious the claimed invention, and Carter and Allan together also fail to make up the deficiencies of the other cited references. For example, neither Carter nor Allan discuss or suggest that conjugating an antibody fragment with one or more non-proteinaceous polymer molecules having actual molecular weights of at least 20 kD would, or would be desirable to, provide a conjugate having an apparent molecular weight of at least about 500 kD as determined by size exclusion chromatography.

Accordingly, Applicants respectfully submit that the rejections of Claims 124-132 under 35 U.S.C. §103(a) as allegedly being obvious over Faanes in view of Zapata and Braxton and further in view of Carter and Allen are overcome.

**The Rejections of Claims 124-132 under 35 U.S.C. §103(a)**

Claims 124-132 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Koumenis in view of Carter and Allan.

Koumenis is presented by the Examiner as discussing a Fab' modified with PEG of molecular weight of 20 and 30 kD and hydrodynamic volumes of 300 kD to 2 million kD, with no loss of bioactivity, the Examiner suggesting that the study allegedly demonstrated the importance of higher molecular weight PEG at fewer sites. As above, Carter is presented by the Examiner as discussing a conjugate of PEG to an anti-HER2 antibody, and Allan is presented by the Examiner as discussing a conjugate of PEG to an anti-CD20 antibody. As discussed above, Carter and Allan together fail to make obvious the claimed invention.

However, Koumenis, dated July 1998, is not a proper reference in view of the priority of the present application, which include priority dates of February 21, 1997 and January 22, 1998 that pre-date Koumenis. Thus, Koumenis may not properly be combined with other references in a rejection under 35 U.S.C. §103(a). Moreover, even were Koumenis a proper reference, it lacks many of the elements of the claimed invention. For example, Koumenis lacks discussion of attachment of a nonproteinaceous polymer molecule to a free sulphydryl group of a cysteine residue within the hinge region of an antibody fragment. Neither Allan nor Carter provide the missing elements.

Accordingly, Koumenis not being properly a prior art reference against the present application, Carter and Allan failing to provide the claimed invention, failing to provide suggestion or motivation to provide the claimed invention, and failing to provide a reasonable expectation of success for the claimed invention, Applicants respectfully submit that the rejections of Claims 124-132 under 35 U.S.C. §103(a) as allegedly being obvious over Koumenis in view of Carter and Allan are overcome.

#### **The Objection to Claim 132**

Claim 132 stands objected to as containing a typographical error. As amended, claim 132 now recites "CD20" and not "DC20" as previously written. Accordingly, applicants respectfully submit that the objection to claim 132 is overcome.

**CONCLUSION**

In conclusion, Applicants respectfully submit that the claims are in condition for allowance, and request reconsideration and allowance of all pending claims.

The Examiner is invited to contact the undersigned attorney at the telephone number indicated below should he find that there are any further issues outstanding.

Please charge any fees, including fees for extension of time, or credit overpayment to Deposit Account No. 08-1641, referencing Attorney's Docket No. 39766-0092 A.

Respectfully submitted,

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